Physiological Relevance of Sodium-magnesium Exchange

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Summary

To investigate physiological relevance of Na^+-Mg^{2+} exchange, we examined the effects of amiloride and ouabain on the regulation of intracellular, free Mg^{2+} concentration ($[Mg^{2+}]_i$) in smooth muscle of the guinea-pig taenia caeci, using nuclear magnetic resonance (NMR) techniques. $[Mg^{2+}]_i$ were mainly estimated from the separation of the α- and β-ATP peaks observed in ^{31}P-NMR spectra. In normal and nominally Ca^{2+}-free solutions, $[Mg^{2+}]_i$ was approximately 0.3-0.4 mM. Application of either amiloride or ouabain in Ca^{2+}-free solutions significantly increased $[Mg^{2+}]_i$ (by approx. 0.5 mM) with only a small change in ATP content. Wash-outs of the drugs reversed the changes in $[Mg^{2+}]_i$. Since changes in pH_i may affect $[Mg^{2+}]_i$ regulation as well as perturb estimation of $[Mg^{2+}]_i$, pH_i during the experiments were estimated using two methods: 1) from the chemical shifts of PME-1 (phosphorylethanolamine); 2) from the chemical shifts of γ- and β-ATP. After correction for pH_i, a significant increase in $[Mg^{2+}]_i$ was still obtained 150 min after application of either drug. In the presence of amiloride simultaneous removal of extracellular Mg^{2+} and Ca^{2+} significantly depleted intracellular Mg^{2+}, as was seen in the absence of amiloride. However, amiloride slowed the speed of the depletion in Mg^{2+}- and Ca^{2+}-free solution. The results suggest the presence of amiloride-insensitive pathway through which Mg^{2+} is passively transported across the plasma membrane. The intracellular Rb^+ concentration was monitored as an index of Na^+-K^+ pump activity, using ^{87}Rb-NMR. The intracellular Rb^+ concentration was hardly changed by amiloride, but reduced to approximately 20% of the control value by additional applications of ouabain. Subsequent wash-outs of ouabain restored the intracellular Rb^+ in the presence of amiloride. These results are consistent with the hypothesis that in smooth muscle, Na^+-Mg^{2+} exchange maintains low $[Mg^{2+}]_i$ using the energy from Na^+-gradient across the plasma membrane. Although many other factors may cause changes in $[Mg^{2+}]_i$, it seems likely that amiloride directly inhibits the Na^+-Mg^{2+} exchanger, whilst ouabain does so indirectly through reduction of the Na^+-gradient across the plasma membrane. These types of the drugs are often used in animal experiments and clinical therapy. Prolonged and chronic applications of such drugs may modulate the cellular response through changes in $[Mg^{2+}]_i$.